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PROPOSED METHODS FOR CONDUCTING SENSITIVITY ANALYSES ON THRESHOLD-DERIVED ESTIMATES OF VALUE-BASED PRICE AND PRODUCT PROFILES FOR EARLY-STAGE DRUGS

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BACKGROUND: Established methods exist for evaluating the effects of uncertainty around the model structure and parameters on the results generated by traditional cost-effectiveness analyses (CEAs) and include one-way and probabilistic sensitivity analyses (SAs). In contrast to the primary outcome of a traditional CEA—the ICER—the primary outcomes of a threshold CEA conducted for a product early in development include (1) the value-based price opportunity given a hypothetical or target product profile and (2) the magnitude of effect required to justify a target price. Because the outputs of a threshold model pertain to a new drug or indication where little or no data have been collected, and because the outputs are multiple, representing the set of product attributes, including price, that will define drug value, there is a need to explore the sensitivity of the results to factors that go beyond uncertainty. In analyses that generate potential value-based price or product attribute levels, new methods and applications of SA are required. **METHODS:** We present example one-way and probabilistic SAs, highlighting problems in interpretation that arise when traditional sensitivity analyses are applied to threshold models. We propose alternative SA methods and analyses and present interpretations of results. a Pricing Contribution Diagram is presented as a means of characterizing the extent to which each product attribute (efficacy, safety, tolerability, quality of life, position in care pathway) influences the value-based price opportunity. Probabilistic SAs are presented to examine the relationship between price (value-based and target) and individual product attributes, and the influence of uncertainty in other model inputs. **CONCLUSIONS:** Traditional methods of conducting SA are insufficient when applied to the threshold application of CEA. Instead, SAs specific to threshold models supporting decisions regarding early stage development should be employed.

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LAST OBSERVATION CARRIED FORWARD (LOCF) VS. MIXED-EFFECTS MODEL REPEATED MEASURES (MMRM): EMPIRICAL EVALUATION OF TWO APPROACHES TO ANALYZING LONGITUDINAL DATA WITH MISSING OBSERVATIONS

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OBJECTIVES: To compare two statistical approaches for analyzing longitudinal data with missing observations: 1)imputation using Last Observation Carried Forward method (LOCF) and 2)Mixed-effects Model Repeated Measures method (MMRM) to analyze the change from baseline in health-related quality of life (HRQoL) by medication adherence level. **METHODS:** HRQoL via SF-12 Health Survey and medication adherence via a 5-level categorical response was measured monthly for one-year for 184 patients in a U.S. multiple sclerosis observational study. HRQoL was summarized in two continuous variables: Physical Component Score (PCS-12) and Mental Component Score (MCS-12). Categorically collected medication adherence was converted to numeric values and average compliance was calculated over a 1-year period then categorized into two groups: ≥90% (GT90) or <90% (LT90) compliant. For validity of compliance, patients who had completed at least 6 measurements during 1-year on compliance question were included. LOCF used the last available change from baseline to impute the missing values for early drop-out. MMRM is a likelihood-based approach which models all actual observations jointly, with no attempt at imputation for missing values. **RESULTS:** A total of 131 patients were included in this analysis. The 12-month change from baseline in PCS-12 comparing patients with GT90 compliance vs. LT90 compliance using MMRM was 0.86 ($p = 0.277$) and using LOCF was 1.30 ($p = 0.339$). For MCS-12, the improvement among patients with GT90 compliance over LT90 compliance using MMRM was 2.04, while the corresponding improvement using LOCF was 1.97. For MCS-12, only the MMRM method produced statistically significant improvements (p-values: LOCF = 0.234, MMRM = 0.026). **CONCLUSIONS:** MMRM and LOCF yielded not only different results but also different statistical significance in the 12-month change from baseline in MCS-12. Since the approach to estimate and model is different between two methods, the pattern and shape of data must be investigated to find the right method to produce valid estimates.

PMC25

STATISTICAL DISTRIBUTIONS OF COST DATA IN PROBABILISTIC SENSITIVITY ANALYSIS

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OBJECTIVES: It is generally agreed that calculation of means after non-linear data transformations (e.g., log-transformation) does not result in a comparison of arithmetic means, and so is not appropriate for cost data in pharmacoeconomic evaluations. This would seem to preclude the use of log-normal distributions for cost data in probabilistic sensitivity analysis. The study objective was to investigate the statistical properties of arithmetic mean costs. **METHODS:** Monte Carlo simulations were use to investigate the statistical properties of arithmetic mean costs derived from an underlying log-normal distribution, $\log_e(X) \sim N(m,s^2)$, where $m = \log_e(€10)$, $s = 1.5$ (range 0.5 to 2.5). An underlying log-normal distribution was used because cost data are typically highly positively skewed. Microsoft Excel was used to perform the Monte Carlo simulations generating 1,000 arithmetic means, each from a sample of N = 100, for each value of s investigated. **RESULTS:** The distribution of arithmetic means increased in positive skewness as s increased. For $s \geq 1.5$, the distribution of arithmetic means deviated considerably from normality. The level of skewness was greatly reduced by use of the log-normal distribution. The Gamma distribution was similar to the log-normal distribution in representing the distribution of arithmetic mean costs. **CONCLUSIONS:** Log-normal distributions for arithmetic mean cost data may have a role for use in probabilistic sensitivity analysis, although this needs further investigation using cost data derived from actual studies.

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EXAMINATION OF TYPE I AND II ERROR RATES IN INTENTION-TO-TREAT RANDOMIZED EXPERIMENTS: DO SUBJECTS NEED TO STAY IN THE GROUP IN WHICH THEY WERE ASSIGNED?

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OBJECTIVES: Intention-To-Treat (ITT) analysis is an established method used in randomized experiments. However, analyzing data where crossover occurs (leaving subjects in the control or treatment arms when they have crossed from one group to another) prevents the true comparison of treatment and placebo effects. When subject's crossover and ITT analysis methods are used, the true effect of the treatment cannot be determined as data from many groups are included with treatment. The purpose of this research is to determine Type I and II error rates computed by simulation results with and without crossover. **METHODS:** A simulation study was conducted to determine the impact of Type I and II error given six crossover percentages (1, 3, 5, 7, 9 and 11%), four effect sizes of treatment based on standard deviation (ES = 0.2, 0.4, 0.6 and 0.8 SD), and four sample sizes (n = 50, 100, 200 and 300). Simulations were conducted using "R" and included 1,000 replications for each sample size, effect size and crossover combination. **RESULTS:** When ES were small (<0.2SD), Type I error rates were below 1%. When ES were larger, and crossover increased Type I rates increased above 4%. Large samples with high crossover and large ES had the highest Type I rates. Type II error rates, which are perhaps more critical, were higher. For 5% crossover, the Type II error rates were 2.4% and for 11% crossover 5.5%. When the ES are very large statistical significance can be observed regardless of crossover percent, even up to 11%. **CONCLUSIONS:** When crossover rates are low and ES are small, researchers can abandon ITT analysis methods and analyze samples as they were treated with little risk of additional Type I and II errors occurring. The benefit of "as-treated" analysis is that the true treatment effect can be determined with little risk of error.

CONCEPTUAL PAPERS & RESEARCH ON METHODS – Patient-Reported Outcomes Studies

PMC27

VALUES FOR HEALTH STATES UNDER DIFFERENT LIFE DURATIONS

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OBJECTIVES: Recent research suggests that the value of health depends also on the time of permanence in a health state. This would imply a more complex relationship between quality and quantity of life than the standard linear relationship assumed in the QALY model. To model whether and how life duration affects the value assigned to health states. **METHODS:** A discrete choice analysis study was conducted comprising health-state scenarios added with a separate duration attribute. Health states were described with the EQ-5D (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), having 3 levels of severity each. Duration was introduced as a sixth domain with six levels (1, 5, 10, 15, 30, 50 years). Sixty choice sets were selected with a Bayesian approach (*Stolk et al., Value in Health, 2010*). a sample of 209 undergraduate students self-completed the computerized response tasks. Data were analyzed with a conditional logistic regression model. **RESULTS:** Main effects show negative preferences towards problems with health domains and positive preference toward longer duration. However, preferences are not linearly related with duration (e.g., the next 41st year is valued less than the next 11^{th} year), but a logarithm function describes more accurately this relationship. Negative interactions are found between health-states and duration. Trends of values for health states with increasing duration are represented by diverging curves: when duration increases, the value assigned to good states increases while the value assigned to bad states decreases. However, due to the logarithm relationship with duration, the marginal (negative or positive) value assigned to any state decreases as duration increases. **CONCLUSIONS:** Duration of health states interacts with the value assigned to them and influences both direction and marginal values through the different durations. Our results show that refinement of the standard QALY framework can be amended.